FOR PUBLICATION

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

DAIICHI PHARMACEUTICAL CO., LTD. and DAIICHI PHARMACEUTICAL CORPORATION, Plaintiffs, v. APOTEX, INC. and APOTEX CORP., Defendants.	Civ. No. 03-937 (WGB) **OPINION**

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BASSLER, SENIOR DISTRICT JUDGE:

In this patent infringement action,[1] Plaintiffs, Daiichi Pharmaceutical Co. Ltd., a Japanese drug manufacturer, and its New Jersey-based subsidiary, Daiichi Pharmaceutical Corporation (collectively, "Daiichi") sued Apotex Inc., a Canadian-based generic drug manufacturer, and its subsidiary, Apotex Corp. (collectively, "Apotex"). Daiichi claims that Apotex infringed on Daiichi's Patent No. 5,401,741 ("'741 patent").

The First Amended Complaint alleges willful patent infringement under the Hatch-Waxman Act, 35 U.S.C. § 271(e)(2), and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, and 35 U.S.C. § 271(a), (b) and/or ©.[2] Apotex denies Daiichi's allegations and raises the following defenses: (1) patent invalidity; (2) anticipation; (3) obviousness; (4) unenforceability; (5) noninfringement; (6) noninfringement of claim 7; and (7) misuse. Apotex filed a counterclaim against

[1]This matter was tried without a jury before this Court on November 1-3, 8-10 and 15-17. Jurisdiction and venue in this district are proper pursuant to 28 U.S.C. §§ 1331, 1338(a), 1391(b) and 1400(b).

[2]In a stipulation dated October 5, 2005, Daiichi agreed, among other things, to dismiss, without prejudice, its second cause of action for a declaratory judgment of patent infringement and for an injunction pursuant to 35 U.S.C. § 283, as pleaded in Daiichi's First Amended Complaint for patent infringement dated May 26, 2004.

Daiichi.[3] Magistrate Judge Arleo severed Counts 7-11 of the counterclaim, which were not directly related to the infringement action and stayed proceedings regarding the severed counts pending trial on the issue of infringement. See September 1, 2004 Discovery and Case Management Order.

For the reasons set forth below, the Court finds that the '741 patent is not invalid or unenforceable. Furthermore, the Court determines that Apotex infringed on Daiichi's '741 patent.

I. FINDINGS OF FACT

These findings of fact constitute the Court's final determination of contested factual issues and therefore supersede any prior recitation of facts contained in Opinions previously entered on the docket. The Court makes these findings of fact pursuant to Fed. R. Civ. P. 52. Before the Court sets forth its findings, it wishes to elaborate on the procedure it utilized to arrive at its factual determinations.

The Court invited the parties to submit proposed findings of fact and conclusions of law, and responses thereto, after the

[3]The 11 Counts of Apotex's counterclaim are: Count 1-Declaration of Invalidity, Count 2-Declaration of Anticipation, Count-Declaration of Obviousness, Count 4-Declaration of Unenforceability, Count 5-Declaration of Infringement, Count 6-Declaration of Non-Infringement of Claim 7, Count 7-Monopolization in Violation of the Sherman Act § 2, Count 8-Attempt to Monopolize in Violation of the Sherman Act § 2, Count 9-Unreasonable Restraint of Trade in Violation of Sherman Act § 1, Count 10-Declaration of Patent Misuse and Count 11-Tortious Interference with a Prospective Business Relation.

close of testimony.[4] The final proposed finding of fact submission was filed February 17, 2006. The Court has carefully reviewed the proposed findings, the documentary evidence and the testimony adduced at trial. The Court, having considered this array of information, sets forth its findings of fact based on its independent review of the evidence and utilizes the parties' proposed findings of fact merely to assist the Court in organizing this information. See 9A Wright & Miller, Federal Practice and Procedure: Civil 2d § 2578 (1995) ("Proposed findings submitted by counsel are no more than informal suggestions for the sole purpose of assisting the court.")

The Court bases its findings of fact on its careful consideration of the testimony adduced at trial and a review of the documentary evidence submitted, as well as the logical inferences to be drawn from them. In evaluating the evidence of record, the Court undertook an individualized assessment of the credibility of each witness and assigned the appropriate weight to the testimony based on the Court's conclusions with respect to

[4]Citations to Plaintiffs' Proposed Findings of Fact or Proposed Conclusions of Law and Defendants' Proposed Findings of Fact or Proposed Conclusions of Law will be cited to as PPFF, PPCL, DPFF and DPCL respectively. Furthermore, citations to the trial transcript ("Trial Tr.") include the name of the witness who was testifying, volume number and page number. Citations to trial exhibits are to Plaintiff's Trial Exhibits ("PTX") and to Defendants' Trial Exhibits ("DTX").

credibility.[5]

To the extent that any of the findings of fact might constitute conclusions of law, they are adopted as legal conclusions. Conversely, to the extent that any conclusions of law constitute findings of fact, they are adopted as factual determinations.

A. The Parties

Daiichi Pharmaceutical Co., Ltd. ("DSK") is a Japanese corporation having its principal place of business in Tokyo, Japan. (Trial Tr. Vol. 2, 101:21-24). DSK is the owner of all right, title and interest in the '741 patent, entitled "Topical Preparation for Treating Otopathy," issued on March 28, 1995. The patent was issued in the name of inventors Kiichi Sato, Akira Handa and Takeji Kitahara – all of Japan, who assigned their right to the patent to DSK. (PTX 1 at 2; PTX 4; PTX 5 at 2,

[5]In assessing the credibility of each witness in this case, the Court has taken into consideration how well each witness was able to recall and describe the things testified to, the manner of the witness while testifying, whether the witness had an interest in the outcome of the case or any bias or prejudice concerning any party or matter involved in the case, whether the witness' testimony was contradicted by what that witness had said or done at another time, by the testimony of other witnesses, or by other evidence and how reasonable the witness' testimony was in light of all the evidence in the case. Miller v. Mercy Hospital, Inc., 720 F.2d 356, 365 (4th Cir. 1983), cert. denied, 470 U.S. 1083 (1985) (citing 9A Wright & Miller, Federal Practice and Procedure: Civil 2d § 2586 (1995))("Credibility involves more than a witness' demeanor and comprehends an overall evaluation of testimony in light of its rationality or internal consistency and the manner in which it hangs together with other evidence.").

patent application number 622, 121; Trial Tr. Vol. 2, 102:8-15; Defendants' Answer to First Amended Complaint dated June 23, 2004 at ¶ 7). DSK is also the holder of New Drug Application ("NDA") No. 20-799 for FLOXIN® Otic (Ofloxacin Otic Solution, 0.3%), which was approved by the U.S. Food and Drug Administration ("FDA") on December 16, 1997. (PTX 31 at DPC-04 00007; PTX 32 at DPC-03 01363; Defendants' Answer to First Amended Complaint dated June 23, 2004 at ¶ 9).

Daiichi Pharmaceutical Corporation ("DPC") is a Delaware corporation with its principal place of business in Montvale, New Jersey and a wholly owned subsidiary of DSK. (Trial Tr. Vol. 2, 101:25-102:4). DPC is the sales and marketing arm of DSK in the United States (Trial Tr. Kane, Vol. 8, 31:9-13). DPC has been and remains the agent of DSK for the filing and regulatory review of NDA No. 20-799 and has an exclusive license to market and sell FLOXIN® Otic in the United States and Puerto Rico (PTX 31 at DPC-04 00007; PTX 32 at DPC-03 01363; Trial Tr. Kane, Vol. 8, 45:23-46:3).

The approved treatment indications for FLOXIN® Otic medicine are i) Otitis Externa in adults and pediatric patients, one year and older; ii) Acute Otitis Media in pediatric patients one year and older with tympanostomy tubes; and (iii) Chronic Suppurative Otitis Media in patients 12 years and older with perforated tympanic membranes, caused by the designated microorganims. (PTX

7C at 2, "Indications and Usage"; PTX 31 at DPC-03 10426; PTX 47 at A000087; PTX 78 at 3, "Indications and Usage").

Apotex, Inc. is a privately held Canadian corporation having its principal place of business in Weston, Ontario, Canada. (Trial Tr. Vol. 2 102:5-7). On or about October 25, 2002, through its Novex Pharma division, Apotex filed Abbreviated New Drug Application ("ANDA") No.76-527 with the U.S. Food and Drug Administration ("FDA") requesting approval to market and sell a generic version of Daiichi's FLOXIN® Otic in the United States for the same FDA-approved treatment indications as FLOXIN® Otic. (PTX 47 at A00001 and 000057; Defendants' Answer to First Amended Complaint dated June 23, 2004 at ¶ 10). Daiichi was given notice by letter of Apotex's ANDA submission pursuant to Section 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act (21 CFR § 314.95(c)) requesting marketing approval to manufacture, use or sell Ofloxacin Otic Solution, 0.3% prior to the expiration of the '741 patent. (Defendants' Answer to First Amended Complaint dated June 23, 2004 at ¶ 11). Apotex Corp. has been designated by Apotex, Inc. to act as Apotex Inc.'s sole agent in the U.S. in all matters relating to the ANDA. (PTX 47 at A000057; Trial Tr. Vol. 2, 103:6-12). Apotex's ANDA included a "Paragraph IV Certification," challenging the validity and infringement of Daiichi's '741 patent. (PTX 47 at A000068).[6]

[6]Since the close of trial, Apotex's ANDA has been reviewed and approved by the FDA on November 18, 2005.

B. '741 Patent

The '741 patent is directed to a method for treating bacterial ear infections by topically administering the antibiotic known as ofloxacin into the ear (PTX 1 at Col. 1, lines 58-64, Col. 5, lines 49-50; Daiichi Pharm. Co., v. Apotex, Inc., 380 F. Supp. 2d 478, 481, 488-89 (D.N.J. 2005)).[7]

[7]The 741 patent sets forth seven claims:

> Claim 1: A method for treating otopathy which comprises the topical otic administration of an amount of ofloxacin or a salt thereof effective to treat otopathy in a pharmaceutically acceptable carrier to the area affected with otopathy.
>
> Claim 2: The method of claim 1 wherein the said otopathy is otitis media.
>
> Claim 3: The method of claim 2 wherein the said otopathy is otitis externa.
>
> Claim 4: The method of claim 2 wherein the concentration of ofloxacin in the pharmaceutically acceptable carrier is about 0.05 to about 2% w/v.
>
> Claim 5: The method as claimed in claim 4, wherein the dosage form of ofloxacin is an aqueous solution.
>
> Claim 6: The method as claimed in claim 5, wherein the aqueous solution of ofloxacin is applied to the external auditory canal by instillation.
>
> Claim 7: The method as claimed in claim 6, wherein the aqueous solution of ofloxacin is intratympanically injected through a puncture in the tympanic membrane.

After holding a Markman hearing on July 22, 2005, the Court held that a person ordinarily skilled in the art would have a medical degree, experience treating patients with ear infections, and knowledge of the pharmacology and use of antibiotics. Daiichi

Ofloxacin is the only antimicrobial compound in Daiichi's eardrops; it has no other active ingredients. (Trial Tr. Klein, Vol. 2, 54:13-24).[8] Daiichi's patented method of treatment covers the use of its FLOXIN® Otic product. (PTX 7C; PTX 78).[9] The 741 patent claims priority from Japanese Patent Application

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Pharm. Co., 380 F. Supp. 2d at 485. Additionally, that person would be a pediatrician or general practitioner-those doctors who are often the first line of defense in treating ear infections. Id. Furthermore, the Court construed the term "otopathy" to mean "bacterial ear infection," the words "effective to treat" to be interpreted as "safe and efficacious," and the phrase "intratympanically injected through a puncture of the tympanic membrane" to mean "introduced into the middle ear with an instrument such as a syringe." Id. at 485-89. Consequently, the parties stipulated that the method for which Apotex seeks approval in its ANDA No. 76-527, "is not within the scope of, or covered by, the literal language of claim 7 of the '741 patent, or an equivalent thereof, as it has been construed by the Court" in the Markman Hearing. (PTX 313 ¶ 4). Subsequently, the parties stipulated that Daiichi would withdraw with prejudice its claim that Apotex's ANDA No. 76-527 infringes Claim 3 of the '741 patent. See March 28, 2006 Stipulation.

[8]Daiichi obtained a patent on the compound of ofloxacin, U.S. patent 4,382,892 ("Hayakawa '892"). (DTX 40; DTX 17 at D0055-64, 70, 71). Daiichi submitted this patent in its application of the '741 patent and acknowledged that it was the assignee of both the '741 and '892 patents. (DTX 17 at D0071). The '892 patent expired on September 2, 2001. 35 U.S.C. § 154(a)(2).

[9]As its title indicates, the '741 patent is a "method" patent, as compared to a machine, composition, or manufacture patent. One treatise explains: "the 'elements' of a method claim, instead of being structural parts, are, and must be, acts or manipulative steps that are performed upon an article, workpiece, or chemical substance. It is the transformation or reduction of the article, workpiece, or chemical substance to a different state or thing that is the essence of a method claim – and the key to its patentability." Robert C. Faber, Landis on Mechanics of Patent Claim Drafting § 4:1(5th ed. 2004).

No. 86378/88, filed in Japan on April 8, 1988. (PTX 1 at 2, left column; PTX 6; PTX 6A; Trial Tr., Vol. 2, 102:16-18).[10]

The '741 patent discloses and claims that the topical otic administration of ofloxacin is safe and efficacious to treat bacterial ear infections (PTX 1 at Col. 2, line 30 - Col. 6, line 55; Trial Tr. Klein, Vol. 2, 35:13-25; Trial Tr. Dohar, Vol. 7, 27:12-16; Daiichi Pharm. Co., 380 F. Supp. 2d at 488). FLOXIN® Otic was the first antibiotic ear drop medicine ever approved by the FDA for treating bacterial ear infections in pediatric and adult patients who have a perforation in their ear drum. (PTX 185 at DSK-06 09300; Trial Tr. Dohar, Vol. 7, 15:1-9; Daiichi Pharm. Co., 380 F. Supp. 2d at 482). Prior to the time of the '741 patent, the available ototopical (ear drop) drugs were known to be ototoxic - i.e., they had a propensity to cause (i) hearing impairment, by damaging the cochlea and its hair cells, and/or (ii) balance impairment, by damaging the vestibular system. (Trial Tr. Klein, Vol. 1, 114:8-24; Trial Tr. Hain, Vol. 3, 119:6-120:8; Daiichi Pharm. Co., 380 F. Supp. 2d at 481-82).

The risk of ototoxicity can occur when an antibiotic compound is applied directly to the middle ear or where the

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[10]This date is critical to Apotex's invalidity argument because prior art that disclosed the elements of the '741 patent claims may anticipate or make obvious the patent, which would invalidate it. Prior art is defined as "that reasonably pertinent to the particular problem which the inventor was involved." Hilton Davis Chemical Co. v. Warner-Jenkinson Co., 62 F.3d 1512 (Fed. Cir. 1995), rev'd on other grounds , 520 U.S. 17 (1997).

tympanic membrane has been ruptured. (Trial Tr. Klein, Vol. 1, 115:1-25).[11] There are, therefore, at least two situations that present the risk of ototoxicity. First is when a patient suffers from *otitis media*, a bacterial infection of the middle ear. Second is when a patient suffers from *otitis externa*, a bacterial infection of the external auditory canal, with a ruptured tympanic membrane.[12] The risk of ototoxicity was present when using ear drops to treat otitis externa because there could be a perforation of the ear drum not appreciated by the physician. (PTX 153 at DSK-06 09694-95 - see "Cortisporin® Otic Solution" - "Precautions"; PTX 314 at 7 ("Otitis externa is easily diagnosed by looking into the external ear with an otoscope. The main problem with diagnosis is deciding whether or not there is also an otitis media, as often one cannot see the ear drum very well as the external ear canal is swollen, painful and filled with debris.")). Therefore, physicians were warned to act with care

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[11]To understand these risks, it is helpful to know that the ear consists of three chambers: (1) the outer ear, including the external auditory canal, which focuses sound waves on the tympanic membrane (commonly known as the ear drum); (2) the middle ear, which conducts sound; and (3) the inner ear, which transmits sound vibrations to the auditory nerve for processing into sound. (Trial Tr. Klein, Vol. 1, 89:19-93:23). The tympanic membrane separates the external auditory canal from the middle ear. (Trial Tr. Klein, Vol. 1, 90:17-91:8).

[12]*Otitis media* and *otitis externa* are characterized by localized pain, swelling, and inflammation. *Otitis externa* is commonly referred to as "swimmer's ear." (Trial Tr. Klein, Vol. 1, 99:4-13; 109:18-20; 114:6-7).

when the integrity of the ear drum was in question. (Trial Tr. Klein, Vol. 1, 115:10-12).

Prior to the time of the '741 patent, none of the available ototopical eardrop preparations were free from the ototoxic safety concern. (Trial Tr. Dohar, Vol. 7, 11:22-12:6; Trial Tr. Hain, Vol. 3, 55:9-57:5; DTX 47 at A006983). All of the otic formulations for ear drops listed in the Physicians Desk Reference ("PDR") carried contraindications to their use in the face of a nonintact ear drum. (Trial Tr. Dohar, Vol. 7, 15:1-9; PTX 153 at DSK-06 09694-95 - see "Cortisporine Otic Solution" - "Precautions"; PTX 315 at 1532 - see "Chloromycetin® Otic" - "Precautions").

Use of systemic antibiotics (absorbed into the bloodstream) also raised the concern of the development of bacterial resistance and other side effects such as diarrhea, vomiting and allergic reactions. (Trial Tr. Klein, Vol. 1, 112:4-113:11; Daiichi Pharm. Co., 380 F. Supp. 2d at 481). Use of systemic antibiotics such as gentamicin and neomycin also were known to cause ototoxic side effects. (Trial Tr. Hain, Vol. 3, 120:9-121:16-122:4; 124:14-24).

In addition, there were no FDA-approved oral antibiotics for use in children to treat ear infections caused by pseudomonas aeruginosa prior to the '741 patent. (Trial Tr. Dohar Vol. 7, 12:7-13:4). Pseudomonas aeruginosa is one of the primary

pathogens that causes ear infections. (PTX 21, 99:9-22; Trial Tr. Klein, Vol. 1, 107:23-108:7; Trial Tr. Dohar, Vol. 7 12:21-13:4).[13] Prior to April 8, 1988, pseudomonas aeruginosa was known to be resistant to amoxicillin[14] and neomycin, which were used to treat bacterial ear infections. (Trial Tr. Dohar Vol. 3, 117:18-24).

The method described in the '741 patent was intended to overcome these risks, by setting forth a method for the topical administration of ofloxacin – a previously known antibiotic compound – to both the external auditory canal and the middle ear, while significantly reducing the risk of ototoxicity and antibacterial resistance. (Trial Tr. Klein, Vol. 2, 13:12-13; 35:19-25; Daiichi Pharm. Co., 380 F. Supp. 2d at 482). Daiichi began conducting tests to establish the safety and efficacy of ofloxacin. (PTX 21 at 203:6-22, 204:4, 204:14-205:9, 205:21-206:14, PTX 218). Changes in auditory brain stem response ("ABR") were measured in guinea pigs, before and after injection of topical ofloxacin otic solution into the middle ear space, and compared to positive and negative controls. (PTX 1 at Col. 2, line 30-Col. 3, line 34, Col. 4, lines 14-38; PTX 21, 75:19-76:5,

[13]Ofloxacin also is effective against other bacteria, including staphylococci aureus and staphylococci epidermis. (DTX 17 at D0379).

[14]Amoxicillin was the most common antibiotic used to fight bacterial ear infection during the period from 1987 to early 1988. Trial Tr. Dohar, Vol. 7, 12:12-14.

80:7-10, 80:18-81:16; Trial Tr. Klein, Vol. 2, 3:13-21, 5:14-12:15). The experimental ABR results showed that topical administration of ofloxacin into the middle ear of guinea pigs caused essentially no ototoxicity; reduction in acoustic acuity (hearing threshold) was also negligible and comparable to the physiological saline negative control. (PTX 1 at Col.2, lines 48-63; Trial Tr. Klein, Vol. 2, 3:13-21, 5:15-12:15, 13:11-14:7).

In contrast, the 4% gentamicin positive control solution administered into the middle ear of guinea pigs caused substantial damage to the hair cells of the cochlea, while the 0.5% ofloxacin solution caused little or very minimal damage. (PTX 1 at Col.4, lines 39-58; Trial Tr. Klein, Vol. 2, 12:3-15). Very little difference was observed in the animals receiving 0.5% ofloxacin solution relative to animals receiving physiological saline control, in terms of seeing no change in the cochlear hair cells of the inner ear, using scanning electron micrographs. (PTX 1, at Col. 4, lines 39-44; Trial Tr. Klein, Vol. 2, 8:6-9; 16:22-18:2).[15]

The ‘741 patent inventors also tested the ofloxacin concentrations in the middle ear mucosa of the animals receiving 0.5% ofloxacin solution to determine whether durable concentrations of drug are achieved at the site of infection in

[15]Scanning electron microscopy is a sophisticated microscopic technique used to get minute details of tissue. (Trial Tr. Klein, Vol. 1, 128:21-23).

order to have an antibacterial effect. (PTX 1 at Col. 3, lines 55-68, Col. 4, line 67 - Col. 5, line 55 (see Table 3 et seq.); Trial Tr. Klein, Vol. 2, 19:12-20:6). The concentration levels of ofloxacin in the middle ear mucosa measured by the inventors showed persistence of the drug at the site of infection. (PTX 1 at Col. 5, lines 1-55 - see Table 3 et seq.; Trial Tr. Klein, Vol. 2, 27:25-28:25). The inventors also demonstrated very limited tissue distribution of the drug outside of the middle ear mucosa, thereby establishing the minimal risk of systemic toxicity from the topical otic administration of ofloxacin. (PTX 1 at Col. 5, line 34-Col. 6, line 1; Trial Tr. Klein, Vol. 2, 19:12-27:13).

The inventors demonstrated that the Minimum Inhibitory Concentration ("MIC")of ofloxacin necessary to inhibit or kill 80% of bacterial strains isolated from patients with middle ear infection was very low (1.56 µg/ml), and their data established that achievable concentrations of ofloxacin at the middle ear mucosa (site of infection) are substantively higher than the 1.56 µg/ml concentration required to inhibit or kill 80% of the microorganisms that might be present at the site of infection. (PTX 1 at Col. 6, lines 5-29 - see Table 4 et seq.; Trial Tr. Klein, Vol. 2, 29:1-30:10, 33:4-35:12).

The topical otic administration of ofloxacin was confirmed to be safe, in terms of hearing and morphology of (lack of damage

to) the cochlear hair cells as measured by ABR and scanning electron microscope, and efficacious for treating bacterial ear infections, in terms of getting a substantive amount of drug at the site of infection compared to what is necessary to inhibit or kill the organism causing the infection. (Trial Tr. Klein, Vol. 2, 35:13-25). The results of the safety and efficacy studies led to the filing of the priority patent application in Japan and the '741 patent application in the United States. (PTX 1 at 2, left column; PTX 6; PTX 6A).[16]

C. Apotex's ANDA Application

In early 2000, Ms. Anita Hui of Apotex, Inc. was assigned the task of preparing an ofloxacin otic solution formulation that was identical to Daiichi's FLOXIN® Otic. (Trial Tr. Vol. 2, 103:2-5). Ms. Cihua Yang, a formulation supervisor at Apotex Inc., instructed one of her formulation chemists, Mohammed Kabir to test FLOXIN® Otic and formulate a generic ofloxacin otic solution product (PTX 19, 12:20-13:18; PTX 23, 17, 15-18:13).

[16]Daiichi filed the original patent application for the '741 patent with the United States Patent and Trademark Office ("PTO") on April 4, 1989. (DTX 17 at D0013-D0015; Trial Tr. Smith, Vol. 5, 35:1-11). As discussed above, the '741 patent claims priority from Japanese Patent Application No. 86378/88, filed in Japan on April 8, 1988. (PTX 1 at 2, left column; PTX 6; PTX 6A; Trial Tr. Vol. 2, 102:16-18). The application which matured into U.S. Patent '741 was filed on April 12, 1993. That application is a continuation of application Ser. No. 892,740 filed on June 1, 1992, which is a continuation of Ser. No. 622-121, filed on Dec. 6, 1990, which is a continuation of Ser. No. 332,913, filed April 4, 1989. (DTX 17 at D0376; Trial Tr. Smith, Vol. 5, 24:11-28:19).

At the beginning of the ofloxacin otic solution project, Apotex obtained samples of Daiichi's FLOXIN® Otic branded product. (PTX 19, 16:19-24; PTX 23, 16:5-17:19). The samples of Daiichi's FLOXIN® Otic were in a box, which stated "FOR USE IN EARS ONLY," and directed the reader to the package insert for "indications, directions and precautions." (PTX 66 at A003237-38; PTX 76 at A003249; PTX 23, 16:13-23).

Ms. Yang reviewed the indications for use of FLOXIN® Otic at that time (PTX 23, 17:7-14). Mr. Kabir obtained the Physicians Desk Reference edition 54 entry for the FLOXIN® Otic product, which describes FLOXIN® Otic's formulation ingredients and indications for use.

On April 28, 2000, Ms. Yang asked Mr. Kabir to test the physical parameters of Daiichi's FLOXIN® Otic product. (PTX 66 at A03236; PTX 23, 17:15-18:7; PTX 18, 66:8-13). Mr. Kabir tested the content, delivery volume, headspace, density, pH, osmalarity, viscosity, surface tension, color, solid content and water content of Daiichi's FLOXIN® Otic on May 2-4, 2000. (PTX 66; PTX 23, 28:5-39:20). Ms. Yang then instructed Mr. Kabir to formulate the first batch of generic ofloxacin otic solution, 0.3% on May 17, 2000, in accordance with the composition of Daiichi's FLOXIN® Otic, as recited in the Physicians Desk Reference, 54th edition, and to compare its physical parameters with samples of Daiichi's FLOXIN® Otic product. (PTX 67 at A003094; PTX 78 at p. 951 -

"Description"; PTX 18, 66:19-68:11; PTX 19, 35:16-37:17; PTX 23 18:8-13).

The formulation work on the generic ofloxacin otic solution, 0.3% was completed by July 10, 2000, one month after Ms. Yang and Mr. Kabir began their formulation efforts by preparing the first 500 ml batch of generic ofloxacin solution. (PTX 19, 74:9-75:19). On October 25, 2002, Apotex submitted ANDA No. 76-527 for Ofloxacin Otic Solution, 0.3% to the FDA. (PTA 47 at p. A00001 and A000057; PTX 17, 25:3-20, 27:12-16, 19-20, 27:23-28:14). Section IV of Apotex's ANDA No. 76-527, entitled "Comparison Between Generic Drug and Reference Listed Drug," sets forth a chart comparing Apotex's generic ofloxacin otic solution, 0.3% to Daiichi's FLOXIN® Otic solution. (PTX 47 at A000108; PTX 17, 37:4-43:18).

The comparison demonstrates that the archive and other ingredients, route of administration, dosage form and strength, and conditions of use (treatment indications) for Apotex's ofloxacin otic solution, 0.3% are identical to Daiichi's FLOXIN® Otic. (PTX 47 A000108; PTX 17, 37:4-43:18). Section IV of Apotex's ANDA No. 76-527 also makes a side-by-side comparison of its proposed package insert for generic ofloxacin otic solution, 0.3% and the package insert for FLOXIN® Otic, in which Apotex's proposed methods of treatment ("Indications and Usage" and "Dosage and Administration") are identical to the FDA-approved

methods of treatment for Daiichi's FLOXIN® Otic. (PTX 47 at A000087-88, A000095-96 and A000098-108; cf. Daiichi's "Indications and Usage", "Dosage and Administration" and "Medication Guide" to Novex Pharma's (Apotex's) "Indications and Usage", "Dosage and Administration" and "Medication Guide"; PTX 17, 40:25-41:16; see also PTX 7C and PTX 78).

Apotex's proposed "Indications and Usage" for generic ofloxacin otic solution, 0.3% in its original ANDA submission are: (i) Otitis Externa in adults and pediatric patients, one year and older; (ii) Chronic Suppurative Otitis Media in patients 12 years and older with perforated tympanic membranes; and (iii) Acute Otitis Media in pediatric patents one year and older with tympanostomy tubes caused by the designated microorganisms. (PTX 47 at A000088 and A000132l PTX 17, 32:13-33:23).

On June 2, 2004, Apotex submitted a Gratuitous Labeling Amendment to the FDA, "carving out" (eliminating) the Otitis Externa indication, leaving Chronic Supportive Otitis Media in patients 12 years and older with perforated tympanic membranes and Acute Otitis Media in pediatric patients one year and older with tympanostomy tubes as the treatment indications for which it seeks FDA approval. (PTX 39 at A006864, A006883, A006891, A006895, A006906-6908, A006920 and A00692l PTX 42 at A006846; PTX 16, 40:24-41:24, 45:11-46:2).

Apotex concedes that the method of administering generic

ofloxacin otic solution is identical to the '741 patent for Claims 1,2,4,5 and 6, but contends that it has not infringed Daiichi's patent '741 because the patent is invalid as anticipated and obvious based on prior art and is unenforceable due to Daiichi's inequitable conduct.

II. CONCLUSIONS OF LAW

A. Invalidity of the Patent

A patent issued by the United States Patent Office is presumed to be valid, and the burden of establishing invalidity rest on the party asserting it. Tokyo Shibaura Elec. Co., v. Zenith Radio Corp., 548 F.2d 88, 93 (3d Cir. 1977) (citing 35 U.S.C. § 282 (1970)). Invalidity must be demonstrated by clear and convincing proof. Universal Athletic Sales Co. v. American Gym, Recreational & Athletic Equip. Corp., 546 F.2d 530, 540 (3d Cir. 1976); see also Merck & Co. v. Teva Pharms. USA, Inc., 228 F. Supp. 2d 480, 496 (D. Del. 2002). "Clear and convincing evidence is evidence that places in the fact finder an 'abiding conviction that the truth of [the] factual contentions are highly probable.'" Merck & Co., 228 F. Supp. 2d at 496 (citing Colorado v. New Mexico, 467 U.S. 310, 316, 104 S. Ct. 2433, 81 L. Ed. 2d 247 (1984)).

This standard is particularly applicable when it appears that the prior art invoked to invalidate a patent has been considered by the Patent Office. Universal Athletic Sales Co.,

546 F.2d at 540, n.28. Apotex claims, however, that Daiichi failed to disclose certain references that are material to this patent infringement suit and argues that the patent is unenforceable because of Daiichi's inequitable conduct. DPFF 107. Apotex further contends that based on the prior art, Daiichi's '741 patent was anticipated and its subject matter was obvious to a person ordinarily skilled in the art.

1. Anticipation

A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003) (citing Lewmar Marine, Inc. v. Barient, Inc., 827 F.2d 744, 747 (Fed. Cir. 1987)). When more than one reference is required to assert invalidity of the claimed invention, anticipation under § 102 cannot be found. Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1282 (Fed. Cir. 2000). There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. Aventis Pharms., Inc., v. Barr Labs., 372 F. Supp. 2d 430, 434-35 (D.N.J. 2005)(citing Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1576 (Fed. Cir. 1991)).

A prior art reference may, however, anticipate without disclosing a feature of the claimed invention if that missing

characteristic is necessarily present, or inherent, in the single anticipating reference. Schering Corp., 339 F.3d at 1377 (citing Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991)). A prior art reference which expressly or inherently contains each and every limitation of the claimed subject matter anticipates and invalidates. See, e.g., EMI Group N. Am., Inc., v. Cypress Semiconductor Corp., 268 F.3d 1342, 1350 (Fed. Cir. 2001).

Apotex argues that the published German patent application, DE 36 32 222 A1 to Grohe ("Grohe '222"), U.S. Patent 4,844,902 to Grohe ("Grohe '902") (collectively "Grohe Disclosures") and Hirota patent 4,923,862 ("Hirota '862") each anticipate the '741 patent. Apotex sought to establish at trial, through extensive testimony from its expert witnesses, that each element of the claims of the '741 patent is disclosed in the Grohe Disclosures or in Hirota '862. (See, e.g., Trial Tr. Robinson, Vol. 4, 3-18, 29-44). The evidence does not support Apotex's position. Although the Grohe Disclosures and Hirota '862 teach certain elements of the claim limitations of the '741 patent, their disclosures are not identical to the '741 patent, nor are the '741 patent's claim limitations inherent in the Hirota or Grohe Disclosures.

Grohe Disclosures

Grohe '222 and Grohe '902 disclose topical preparations of

gyrase inhibitors, which are a class of antibacterial compounds. (DTX 17 at D245-49 and D275-292; DTX 21 at Col. 1:6-10 (A6611) and Cols. 17-34 (A6619-6627); Trial Tr. Dohar, Vol. 7, 143:19-144:18). The only difference between Grohe '222 and Grohe '902 is that the topical preparations discussed in Grohe '902 additionally comprise a corticosteroid.[17]

Grohe '222 teaches that ofloxacin is among the group of gyrase inhibitors that can be "applied topically as topical preparations for the treatment or prophylaxis of infections, diseases and injuries of the skin . . . [as well as] deep or systemic infections." (DTX 17 at D0251). Grohe '222 discloses that gyrase inhibitors can be applied in the topical preparations as such or "as salt with an acid base." (Id.) Grohe '222 further discusses that the topical preparations can be used in several forms, including solutions. (Id. at D0252). Claim 1 of the Grohe patent application states that "[a] topically applicable formulation comprising weight about 0.05 to 30% of an antibacterially active compound . . ." should be used. (Id. at D0247).

Grohe '222 adds that topical preparations of the invention are especially effective against bacteria and bacteria-like microorganisms, including staphylococci aureus, staphylococci

[17]Since all claim limitations of a patent must be contained in a single prior art reference for the patent to be anticipated by that reference and because Grohe '222 and Grohe '902 are essentially the same, only Grohe '222 will be discussed here.

epidermis, streptococci pneumonia, hemophilus influenzae, pseudomonas aeruginosa, which are all bacteria known to cause otitis media and otitis externa. (Id. at D0273; see also DTX 375, Table 4; see supra 12). Furthermore, the Grohe patent application discloses that besides humans, bacterial infections can also be treated in other animals and lists otitis as a bacterial infection that can be treated in dogs and cats. (Id. at D0274).

Dr. Joseph R. Robinson, Apotex's expert witness on the design and development of opthalmic preparations and opthalmic drug delivery systems, testified that the element of Claim 1 of the '741 patent disclosing "an amount of Ofloxacin or a salt thereof [safe and efficacious] to treat [bacterial ear infection]" is taught by page D0251 of the Grohe patent application, which states that "gyrase inhibitors [including ofloxacin] can be applied in topical preparations as such or as salt with an acid or base." (Trial Tr. Robinson, Vol. 2, 135:8-16). The Court does not find these disclosures identical. More specifically, the Court finds that a person ordinarily skilled in the art would not infer from this disclosure or from any other disclosures in Grohe '222 that ofloxacin is safe to treat bacterial ear infections as is taught in Claim 1 of the '741 patent.

Dr. Robinson further testified that the safety of the use of

Ofloxacin is indicated by the disclosure of Grohe '222, which states that "[f]or low toxicity the topical preparation according to the invention show a wide antibacterial spectrum against Gram-positive and Gram-negative germs." (Trial Tr. Robinson, Vol. 2, 137: 5-17; DTX 17 at D0272). He explained that "[t]oxicity is a relative term" which refers to the range at which the concentration of a drug exceeds therapeutic effectiveness and becomes toxic. (Trial Tr. Robinson, Vol. 2, 138:21-23). Robinson stated that an agent that has low toxicity generally has a low lethal dose and low sensitization, photosensitization or antigenicity.[18] (Id. at 138:13-20; 139:5-8).

Dr. Hain, Apotex's expert witness testifying in the field of neurology and ototoxicity, explained that Grohe's discussion of the systemic toxicity of Ofloxacin concerned how much Ofloxacin would be needed in order to kill a mouse. (Trial Tr. Hain, Vol. 3, 43:19-21). He clarified that photosensitization regards whether a preparation put on the skin becomes more vulnerable to the sun, which is not relevant to the treatment of the external ear cavity. (Id. at 43:1-3). He added that antigenicity meant that "people do not become allergic to that preparation." (Id. at 43:12-14). As discussed below, these concerns are not

[18]Grohe actually does no reference sensitization, photosensitization or antigenicity. These terms are, however, discussed in the Hirota patent application. (PTX 28 at A006609).

equivalent to the hearing loss and tissue distribution safety concerns that affect the ear. (See infra at 29-30).

Dr. Robinson further maintained that Claim 6 of the '741 patent, which refers to an "aqueous solution of ofloxacin being applied to the external auditory canal by instillation," is "intuitively obvious." (Trial Tr. Robinson, Vol. 2, 149:3). He testified that Claim 6 merely refers to the instillation of a dosage unit or drop into the ear to treat an ear infection and is present in any application that discusses topical administration, especially in a solution form. (Id. at 3-17). He noted that Grohe '222 "mention[s] the term solutions . . . on D0252" and water being used with solutions on D0270. (Id. at 147:18-19; 148:8-15). He further testified that Grohe '222 teaches that "[t]he present invention also includes pharmaceutical preparations in dosage units," and that the invention can be used to treat otitis in dogs and cats. Based on all of these disclosures, Robinson concluded that Grohe '222 clearly discloses that an ear drop is instilled into the ear as taught by Claim 6 of the '741 patent.

The Court is not persuaded by Apotex's piecemeal attempt to show that the Grohe '222 is identical to the '741 patent. The Court finds that a person ordinarily skilled in the art would not have concluded based on the several sections of the Grohe patent application relied on by Apotex, that Grohe '222 teaches the safe

and efficacious treatment of ofloxacin topically administered to the ear prior to April 8, 1988. Glaxo Group Ltd. v. Teva Pharm. USA, Inc., C.A. No. 02-219 GMS, 2004 U.S. Dist. LEXIS 16750, at *36 (D. Del. August 20, 2004) ("Drawing this conclusion . . . requires several leaps, which the court finds would not have been taken by a person of ordinary skill in the art on or before June 25, 1985").[19] Cherry picking sections from different pages of the Grohe '222 patent application that are not necessarily related, does not satisfy Apotex's burden to show by clear and convincing evidence that Grohe '222 anticipates the '741 patent.

To render a patent invalid, an anticipating reference must describe the patented subject matter with sufficient clarity and detail to establish that the subject matter existed and that its existence was recognized by persons of ordinary skill in the field of the invention. ATD Corp. v. Lydall, Inc., 159 F.3d 534, 545 (Fed. Cir. 1998). Anticipation is not established if it is

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[19]Grohe '222 further teaches that the gyrase inhibitors can be used to treat injuries of the skin. (DTX17 at D0251). Robinson testified that the external auditory canal is skin, but noted that the skin right on the outside of the ear has some differences in the composition of the glands that constitute the tissue inside the external ear canal. Robinson nevertheless concluded that the external auditory canal is "basically an extension of the skin." (Trial Tr. Robinson, Vol. 4, 18:15-17). This testimony exemplifies the types of analytical leaps continuously made by Apotex. Such analytical leaps are not sufficient to satisfy Apotex's burden. Glaxo Group Ltd., C.A. No. 02-219 GMS, 2004 U.S. Dist. LEXIS 16750, at *1 (prior art establishing that drug could be used to treat migraine did not anticipate method of using drugs to treat nausea and emesis, which were symptoms of migraines).

necessary to pick, choose and combine various portions of the disclosure not directly related to each other by the teachings of the reference in order to show that the claims of the patent at issue are identically disclosed in the prior art. Application of Arkley, 455 F.2d 586,587-88 (Cust. & Pat. App. 1972) ("Such picking and choosing may be entirely proper in the making of a 103, obviousness rejection . . . but it has no place in the making of a 102, anticipation rejection."). Therefore, Apotex has failed to show by clear and convincing evidence that Grohe '222 anticipates the '741 patent.

Hirota '862

The Hirota '862 patent, entitled "Topical Preparation Containing Ofloxacin," was filed on December 17, 1987 and was issued May 8, 1990. Hirota teaches that ofloxacin, which was disclosed as an "excellent antimicrobial agent" in the Hayakawa '892 patent, had been chiefly administered as an oral agent. (DTX 28 at A006607, Col. 1, lines 16-18). Hirota discloses, however, that ofloxacin or its optical isomer also can be utilized as topical preparations. The claims of the Hirota patent are directed to topical hydrogel or oil-in-water cream preparations containing ofloxacin or "a pharmaceutically acceptable salt thereof." (DTX 28).

A variety of dose forms and bases can be applied to the topical preparations according to the Hirota patent. Hirota

discloses, however, that hydrogels and creams are superior in absorbability to general ointments that use vaseline or other bases, which have low percutaneous absorption. (Id. Col. 1, lines 50-58). Percutaneous absorption describes a drug's absorption through the skin into the blood for preparations such as opthalmic ointment preparations. (Trial Tr. Hain, Vol. 3, 60:23-61:12; DTX 28 at A006607, Col. 1, lines 59-61). The Hirota patent teaches, however, that its inventions do not always require percutaneous absorption.

Hirota '862 discloses that the topical preparations of the invention are administered by directly applying an appropriate amount to the affected part, or spread on sterilized gauze and attached to the skin. The patent identifies several bacteria that the invention exhibits potential antimicrobial activities on, including staphylococcus, streptococcus pyogenes, pseudomonas aeruginos, heomophylus influenza, bacteria known to cause otitis media and otitis externa, noting that the invention is expected to produce "excellent therapeutic effects on skin diseases caused by these microorganisms." (DTX 28 Col. 6, lines 10-21).

Like it does with Grohe '222, Apotex picks and chooses elements of Hirota in an effort to invalidate the '741 patent on the basis of anticipation. Hirota, unlike Grohe '222, does not even disclose the treatment of otitis in dogs and cats, but states that the topical preparation of ofloxacin, in hydrogel and

oil-in-water cream preparations, was useful for treating and preventing infection in nasal or auricular cavities. Id. The Court does not credit Robinson's testimony that the auricular cavity includes the external auditory canal (Trial Tr. Robinson, Vol. 4, 38:1). Even if the Court did accept this opinion, a person of ordinary skill in the art would not know from the Hirota disclosures that the topical preparation of ofloxacin is useful, let alone safe, for the treatment of bacterial ear infections. Therefore, Apotex has not shown by clear and convincing evidence that Hirota anticipates the '741 patent.

Lack of Ototoxicity Disclosure

Apotex notes, and the Court agrees, that the claims define the invention, and it is the claims, not the specifications, that are anticipated. Constant v. Advanced Micro-Devices, Inc., 848 F.2d 1560, 1571 (Fed. Cir. 1988). Based on that proposition, Apotex argues that the fact that Grohe and Hirota do not discuss "ototoxicity" does not preclude anticipation because "ototoxicity" is not an element of the claims in the '741 patent. (See Defendants PCL 109). Although the claim limitations of the '741 patent do not expressly state the word ototoxicity, they disclose "a method for treating otopathy which comprises the topical otic administration of an amount of ofloxacin or a salt thereof 'effective' to treat otopathy." (DTX 375 at D0379, Col. 6, lines 36-39). The Court has construed the word "effective" to

mean safe and efficacious finding that "[s]afety was a paramount concern of the inventors" of the '741 patent. Daiichi Pharm. Co., 380 F. Supp. 2d at 488.

Grohe '222 discloses nothing regarding the safe topical otic administration of an amount of ofloxacin to treat otopathy. Although Hirota teaches that the topical hydrogel and cream preparations, when applied to the skin, did not cause any problems of antigenicity, skin sensitinogenicity, and photo sensibilisinogenicity, these are not the paramount safety concerns that are at issue when discussing otopathy. See supra 25. Ototoxicity and minimal tissue distribution in the blood serum, central nervous system and inner ear perilymph are. Therefore, unlike the In re Aventis Pharms., Inc. case cited by Apotex to support its position, the Court finds that the safe topical administration of ofloxacin is a claim limitation that is imparted by the characteristics or properties of the patent. Cf. 372 F. Supp. 2d 430, 439 (D.N.J. 2005) (concluding that the presence of a separate intragranular disintegrant which is distinct from a tablet without a separate intragranular disintegrant was not a claim limitation and could not preclude a finding of anticipation). Since Apotex has provided no evidence that Grohe or Hirota disclose the safe, non-ototoxic topical use of ofloxacin, it has failed to meet its burden of proof.

2. Obviousness

A patent may be deemed invalid if it is "obvious." Under 35 U.S.C. § 103, "[a] patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains." Put simply, an invention is invalid if "the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent." Glaxo Group Ltd., 2004 U.S. Dist. LEXIS 16750, at *29 (citing Graham v. John Deer Co., 383 U.S. 1,15, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966)) In Graham, the Supreme Court established three criteria that the courts must consider to determine whether a patent is obvious: 1) the scope and content of the prior art, 2) differences between prior art and claims at issue and 3) the level of ordinary skill in the pertinent art. 383 U.S. at 17-18; see also Universal Athletic Sales Co., 546 F.2d at 541. The Supreme Court further set forth permissive or secondary criteria that courts should weigh in determining whether a patent is obvious, including commercial success, long felt but unsolved needs and failure of others. Graham, 383 U.S. at 17.

Apotex argues that based on the prior art and in particular, Grohe '222, Hayakawa '892, Hirota '862, Katz '456, and the Ganz

article[20] and the two Lenarz articles,[21] patent '741 is obvious. Daiichi maintains that none of these materials disclose the topical otic administration of ofloxacin for the safe and efficacious treatment of otopathy or bacterial ear infections. The Court agrees.

First, the Hayakawa '892 patent only discloses the compound ofloxacin.[22] Although Apotex suggests that Daiichi merely seeks to extend the Hayakawa '892 patent, Hayakawa did not disclose the topical otic administration of an amount of ofloxacin safe and efficacious to treat bacterial ear infection. (See Trial Tr. Vol. 1, 62:22-63:14). Second, as discussed earlier, neither Grohe '222 or Hirota '862 teach that the topical administration of ofloxacin to the ear is safe.

Third, U.S. Patent No. 4,551,456 ("Katz '456 patent") was

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[20]Ganz, H. "Gyrase inhibitor in local treatment of chronic bacterial infection in radical middle ear cavities," (1986) H.N.O. (*West Germany*) 34:511-514.

[21]See Lenarz, T. "Chemotherapy of Otitis Media with Ofloxacin" (1987) Drugs 34:139-143 (supp. 1); Lenarz, T. "Ofloxacin in Oral Chemotherapy of Acute and Chronic Otitis Media" (1986). Infection 14:s324-326.

[22]Specifically, the '892 patent teaches that compounds [including ofloxacin] "are effective anti-bacterial agents for treatment against various infectious diseases such as urinary tract infections or infections in respiratory organs in mammals including humans." (DTX 17 at D0063, column 12, lines 10-13). It further notes that although the compounds are used normally by oral administration, they can be administered by injection or by "external application depending upon the type of diseases to be treated." (DTX 17 at D0055 and D0063, Col.12:13-17).

issued November 5, 1985 and described the treatment of a wide variety of bacterial eye infections by the topical administration of norfloxacin and related antibiotics such as ofloxacin. (DTX 17 at D0065, Col. 1, lines 15-18, 31). The patent examiner rejected the '741 patent five times based on the Katz patent, reasoning that Katz '456 teaches that ofloxacin "is effective against a broad spectrum of gram positive and gram negative organism[s]" and can be topically administered to treat bacterial infections including those in the ear. (DTX 17 at D0055, D0085-86, D0190-91, D0294-95, D0333-34).[23]

Katz, like Hayakawa, Grohe and Hirota, may have disclosed that the topical otic administration of ofloxacin would be effective to treat otopathy, however, it did not teach that ofloxacin could be topically administered to the ear to treat otopathy safely. This distinction may seem minor, however it is critical in this case where the Court specifically construed the word effective in the '741 patent to mean "safe and efficacious." Daiichi Pharm. Co., 380 F. Supp. 2d at 488.

For instance, Daiichi submitted a declaration in response to the fourth of the five rejections by the patent examiner. Daiichi explained that Katz could not be used to reject the '741

[23]In the first rejection, the examiner actually denied the '741 patent application, which consisted of only one claim: "[a] topical preparation for treating otopathy which contains ofloxacin or a salt thereof as an active ingredient as disclosed" as anticipated by Katz. (DTX 17 at D0055).

patent because while there is only a small increase in clinical effect between oral versus topical administration of ofloxacin to treat the eyes, studies showed a large increase in the clinical effect when using topical administration of ofloxacin to treat the ears versus oral administration. (DTX 17 at D0300-302). Nevertheless, the patent examiner rejected the '741 patent a fifth time stating that "the declaration shows a comparison of oral vs topical administration but the Katz patent teaches topical administration." (DTX 17 at D0333).

The patent examiner, however, allowed Daiichi's '741 patent to issue after Daiichi submitted its request for reconsideration dated September 26, 1994. This request not only discussed the distinction between the efficacy of oral versus topical administration of ofloxacin in the eyes and ears, but also disclosed the reduction in side effects, especially hearing toxicity, of the drug and the distribution of the drug to the affected area in adults and children based on the tests conducted by the inventors.

Although the patent examiner never stated explicitly why he allowed the '741 patent to issue, he noted on the form issuing the patent that "this communication is responsive to [Daiichi's] 9-26-94 [request for reconsideration]." (DTX at D0368). Apparently, something in the September 26, 1994 request for reconsideration convinced the patent examiner to change his mind

after five rejections; the Court is persuaded that the lack of any disclosure regarding the safety of ofloxacin topically applied to the ear in Hayakawa, Grohe, Hirota or Katz prevents this Court from finding that the '741 patent was obvious.

Similarly, the other articles and documents relied on by Apotex do not disclose the safety element of the patent. In the Lenarz 1986 article titled "Ofloxacin in Oral Chemotherapy of Acute and Chronic Otitis Media," Lenarz discusses a clinical study performed to evaluate the efficacy and safety of ofloxacin through oral administration to middle ear infections. (DTX 50 at S 324). Lenarz noted that ofloxacin caused a very low rate of adverse effects, especially recognizing the absence of ototoxicity. (Id. at S 326). The article, however, did not mention the topical administration of ofloxacin to treat bacterial ear infections.

Daiichi submitted the Lenarz 1986 reference to the Patent Office Examiner during the examination of the '741 patent application, but Daiichi did not include a copy of the article written by Lenarz in 1987. (DTX 17 at D109; number 4 "INFECTION, Vol. 14, Suppl. 4, 1986" is Lenarz 1986; see also DTX 60). This article is a later version of the Lenarz 1986 article. In contrast to the Lenarz 1986 article, however, the Lenarz 1987 article ends by stating that "[e]ardrops containing ofloxacin should also be tested for the efficacy and possible ototoxicity."

(Trial Tr. Hain, Vol. 3, 86:18-21; DTX 60 at 142).

Apotex itself admits that the last sentence of the Lenarz 1987 article "expressly suggest[ed] to **try** Ofloxacin as an ear drop." DPFF 66(d)(emphasis added). "Obvious to try" is not the standard for obviousness and has long been held not to constitute obviousness. In re Roemer, 258 F.3d 1303, 1310 (Fed. Cir. 2001).

> An "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.

In re Eli Lilly & Co., 902 F.2d 943, 945 (Fed. Cir. 1990).

The Court is persuaded by Dr. Dohar, Daiichi's rebuttal expert witness, who testified that Lenarz was "pointing out the very real difference between an oral systemic administration and a topical administration" when he commented that eardrops containing ofloxacin should be tested for ototoxicity. (Trial Tr. Dohar, Vol. 7, 17:10-12). Dr. Dohar further testified that "[Lenarz] understands primarily the fact that with topical administration, there would be a much higher concentration of antibiotic that would be exposed to the ear." (Id. at 17:12-15).

The Court finds that a person ordinarily skilled in the art would not conclude from the Lenarz article discussing the safety of oral or systemic ofloxacin that topically administered ofloxacin would be safe to treat bacterial ear infections.

Furthermore, a person ordinarily skilled in the art would learn from the Lenarz article that topically administered ofloxacin to the ear must be tested to determine its safety.

Lenarz, nor any other prior art cited by Apotex, contains tests that confirm ofloxacin's safety when applied topically to the ear, which this Court finds is necessary to prove by clear and convincing evidence that the '741 patent is obvious. See Chiuminatta Concrete Concepts, Inc., v. Cardinal Indust. Inc., 145 F.3d 1303 (Fed. Cir. 1998) (Patent which claimed method of cutting concrete at time before concrete had reached specified range of hardness was not invalid for obviousness absent evidence establishing that tests–described in report providing recommendations for cutting highway concrete–were indicative of work that existed in the prior art.).

Furthermore, in the Question/Answer portion of the Lenarz article, Lenarz was asked to compare a locally administered quinolone such as ofloxacin with other locally applied drugs. Lenarz responded that "[s]ubstances that are effective against Pseudomonas, particularly gentamicin and neomycin, tend to cause ototoxicity. This has not been a problem in or experience with **oral** Ofloxacin." (DTX 60 at 142) (emphasis added). Again, Lenarz's statement focused solely on the safety of oral ofloxacin and supported Daiichi's contention that ototoxicity caused by drugs available to treat bacterial ear infections at the time was

a concern of physicians. Lenarz further stated in response to that question that "in otitis externa, the infection is localized under the skin and it is not treatable with ear drops," actually "teaching away" from the '741 patent. (DTX 51 at 142-43; Trial Tr. Dohar, Vol. 7, 23:19-24:10).

A prior art reference that "teaches away," or discourages the practice of the invention, supports the nonobviousness of the invention. In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994). The Ganz article also relied upon by Apotex, teaches away from the '741 patent. The article, which was written in German but has an English abstract, describes a clinical study of patients suffering from chronic bacterial ear infections (18 infected radical cavities, 2 external otitis) that were treated with a gyrase inhibitor (Ciprofloxacin) solution. (DTX 52 at DSK-01 00635; DTX 17 at D0422). The bacterial infections were cured in 17 out of 20 cases in the study. (Id.).

Although Ganz does not mention ototoxicity, he reports that no side effects were seen. (Id.). Ganz also notes, however, that gyrase inhibitors such as Ciprofloxacin are antibiotics of second choice. Ganz adds that for local treatment in the ear gyrase inhibitors "should be used only in difficult cases and exclusively by the otologist." (Id.). Therefore Ganz's disclosure does not support Apotex's argument that a person ordinarily skilled in the art would know that the use of

ofloxacin, a gyrase inhibitor, to treat bacterial ear infections topically is both efficacious and safe.[24]

As discussed above, safety is an element of the '741 patent claims. The Ganz article cited by Apotex stresses the safety concerns of using gyrase inhibitors. The Lenarz 1987 article

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[24]Apotex makes two additional arguments that the Court finds are not persuasive. Apotex contends that physician's use of eye drops in the ears prior to April 8, 1988 and the use of ofloxacin tablets for oral ear infections anticipate and make obvious the '741 patent. Apotex claims that a person of ordinary skill in the art would have known ofloxacin was known to be safe in the ear because it was safe for use in the eye according to the product sheet for TARAVID® (ofloxacin) Eye Drops. See DPFF 56 (citing DTX 17 at 405-06). Apotex further contends that doctors had been using eyedrops to treat ear infections for years. See DPFF 17-19, 56, 103. First, as Dr. Kitahara, one of the patent inventors, noted, even if physicians were using eye drops for use in the ear, they did so off-label, without the support of any safety studies and thus at the risk of impairing their patients' hearing. (DTX 195, Kitahara 11/13/03 Dep. at 227:20-24; 233:21-234:10; 234:24-235:11, 236:18-21, 237:11-240:17). Second, Apotex must show by clear and convincing evidence that the Taravid product sheet was publicly available to a person of ordinary skill in the art prior to the critical date of the invention for it to be considered prior art. Makurkar v. C.R. Bard, Inc., 79 F.3d 1572, 1578 (Fed. Cir. 1996) ("Bard must persuade the trier of fact by clear and convincing evidence that the Cook catalog was published prior to Dr. Makurkar's invention date."). Apotex has not shown by clear and convincing evidence that the product sheet for TARAVID® Eye Drops was ever even published, let alone that it was made publicly available prior to the April 8, 1988 critical date. (DTX 17 at 400-06; DTX 54 at DSK-01 44-45). In addition, ofloxacin eye drops were not approved for use in the United States until 1993. (Trial Tr. Robinson, Vol.4, 98:14-99:24). Furthermore, Apotex cannot rely on the use of ofloxacin tablets in Japan to strengthen its argument that ofloxacin was safe for use in the ear. "Knowledge or use of a device in a foreign country, such as Russia, without such knowledge or use in this country, is not a statutory bar to the patent in suit." Badowski v. United States, 164 F. Supp. 252, 255 (Ct. Cl. 1958). Ofloxacin tablets have yet to be approved for use in the United States. (Trial Tr. Klein, Vol. 2, 43:22-44:2).

also clearly states that studies should be conducted in order to test the ototoxicity of administering ofloxacin topically to treat otitis media. Furthermore, neither Hayakawa, Katz, Hirota or Grohe establish the safety of treating otopathy topically. The Court, therefore, finds that Apotex has not proved by clear and convincing evidence that the '741 patent is invalid for obviousness.[25]

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[25]Secondary considerations further support the Court's finding that the '741 patent is non-obvious. Trio Process Corp. v. L. Goldstein's Sons Inc., 461 F.2d 66, 70-73 (3d Cir. 1972) ("Such secondary considerations as commercial success, long felt but unsolved needs and failure of others, etc. might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented."). The evidence shows that Daiichi's FLOXIN® Otic product was commercially successful considering that its market share increased from 0.1 percent to 20 percent within the first five years. (Trial Tr. Kane, Vol. 8, 59:1, 113:11-19). Further evidence of FLOXIN® Otic's success is demonstrated by the decrease in the market share of Cortisporin® Otic, a drug with name recognition with a brand name sold since 1970 and Cortisporin® Otic's generic equivalents, which declined from about 75-80% to 45% of the ototopical market. (Id., 53:5-9, 126:18-22). The Court finds that '741 patent also satisfied a long felt medical need by providing physicians with a non-ototoxic alternative to the available drugs to treat bacterial ear infections. The '741 patent also did not cause the same safety concerns of side effects, bacterial resistance, irritation of the middle ear mucosa and concentration of the drug absorbed in the blood stream, central nervous system and inner ear perilymph as did conventionally available antibiotics. (PTX 139 at DSK-06 9591, left-hand column; DTX 194, Kitahara Dep. (11/12/04) at 109:6-15, 112:2-20; Trial Tr. Klein, Vol. 2, 20:7-21:12). Dr. Hain, Apotex's expert, suggested that ototoxicity was not a critical concern of physicians testifying that physicians used medications that "contained compounds known to have systemic ototoxicity . . . liberally." (Trial Tr. Hain, Vol. 3, 57:2-11). His own expert report, however, states that "ototoxicity associated with the systemic use of aminoglycosides such as Gentamicin has led practitioners to have concerns regarding the risk of ototoxicity from these drugs when applied topically." Id. at 122:19-123:4. Furthermore, Dr. Hain admits

3. Inequitable Conduct

Applicants for patents and their representatives must prosecute patent applications in the PTO with candor, good faith and honesty. Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995). This duty is codified in 37 C.F.R. § 1.5, which provides that:

> each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability.

A party asserting that an applicant breached the duty of candor to the patent office must show by clear and convincing evidence (a) an intent to mislead and (b) either the concealment of non-cumulative prior art known to be material or an express misrepresentation to the PTO. Nordberg, 82 F.3d at 397; see also Pharmica Corp. v. Par Pharm. Inc., 417 F.3d 1369, 1373 (Fed. Cir. 2005). Apotex argues that patent '741 is unenforceable because Daiichi wrote the incorrect date on a form submitted to the examiner disclosing the Grohe application and failed to disclose the Hirota patent, which were both material to the patent examiner's review. Although the documents may have been material

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that Ofloxacin Otic Solution is safer than Cortisporin Otic Solution and that he recommends using the Ofloxacin Solution instead of ototoxic aminoglycosides whenever possible. Id. at 132:22-133:4.

to the '741 patent application, the Court rejects Apotex's claim that the patent is unenforceable due to Daiichi's conduct.

Grohe '222

On June 1, 1992, Daiichi submitted to the PTO a copy of Chemical Abstract No. 110 page 29110 for the Grohe '222 reference and an Information Disclosure Statement ("IDS") listing that abstract. (DTX 17 at D0178 and D0186; Trial Tr. Smith, Vol. 5, 162:3-13). On April 12, 1993, Daiichi submitted the German language original and a full 49-page English translation of Grohe '222 as part of another IDS, in which Daiichi directed the examiner's attention to the disclosure of Grohe '222. (DTX 17 at D0243-292; Trial Tr. Killworth, Vol. 6, 120:10-18).

On the PTO Form 1449 submitted with the IDS, the applicants wrote the incorrect publication date of the Grohe patent application. (DTX 17 D0216). The applicants typed that the German application was published 7/7/88, instead of typing 4/7/88, which was one day before the April 8, 1988 priority date of the '741 patent. (Id.). The examiner drew a line through the German patent listing of Grohe '222 on the PTO Form 1449, with the incorrect typed date, signifying that he had not considered the German application in his examination. (Trial Tr. Smith, Vol. 5, 34:5-25). Beside the English translation of the German Patent, however, the examiner initialed the translation representing that he had considered it and dated the listing

using the incorrect date that the applicant had typed on the form. (Id.). The Government Printing Office then put July 7, 1989, as the publication date for the Grohe patent application on the face of the Daiichi '741 patent, making yet another mistake as to the publication date of the Grohe patent. (Trial Tr. Smith, Vol. 5, 126:22-127:17; Trial Tr. Killworth, Vol. 8, 19:15-21:9).[26] Daiichi never took any steps to correct the wrongly listed date. (Trial Tr. Smith, Vol. 5, 108:21-110:5).

Apotex contends that an inference of intent can be drawn from what its expert, Dr. Smith, who had worked at the PTO for 33 and a half years, refers to as Daiichi's "three false representations." (Trial Tr. Smith, Vol. 6, 55:23-24). Smith explains that Daiichi made two false representations when they stated on the IDS that Grohe '222 contains "no disclosure of topical preparations for the ear **as is the case with the present invention**," and does not suggest that solutions can be applied to the external auditory canal or injected intratympanically. (DTX 17 at D0243) (emphasis added). Smith claims that Daiichi made its third false representation by dating the German patent application with the wrong date, typing 7/7/88 instead of 4/7/88.

The Court is not persuaded that Daiichi's statements about

[26]Although it is uncertain why the Government Printing Office put the date as July 7, 1989, the handwritten 7/7/88 date, written by the patent examiner on the 1449 form was somewhat illegible.

the Grohe patent application constitute false representations, which were intended to deceive the patent examiner. Grohe '222 suggests that gyrase inhibitors, which includes ofloxacin, can be used to treat otitis in dogs and cats and that solutions–along with creams, sprays, etc.–are types of dosage forms suitable for topical preparations (which is noted several pages before the statement regarding otitis). (DTX 17 at D0251, D0270, D0274). Grohe's disclosures do not necessarily teach that an ofloxacin solution may be topically administered to the external auditory canal or injected intratympanically to treat bacterial ear infections safely and efficaciously as disclosed in the '741 patent. Not only are Daiichi's statements to the patent examiner justified, but Daiichi is entitled to disagree with Apotex's interpretation of Grohe '222, which is not clear from the face of the patent application.

The Court further does not find that there is clear and convincing evidence that Daiichi intended to mislead the examiner by typing the incorrect date on the IDS. Apotex has not submitted clear and convincing evidence that the typed incorrect date was anything more than a typographical error. (DTX 223, Olexy 12/17/03 Dep. at 160:24-161:23; DTX 17 at D0216). The correct April 7, 1988 date was clearly written on both the German and English translations of the application. (DTX 17 at D0217, D0245; Trial Tr. Smith, Vol 5, 159:22-160:10). The examiner did

not draw a line through the English translation of the PTO Form 1449, which indicated that he had reviewed that translation putting him on notice of the correct date. (Trial Tr. Smith, Vol. 5, 34:5-25; see supra at 42).[27]

Furthermore, the Chemical abstract submitted by Daiichi had the correct date of the application on it. (Trial Tr. Smith, Vol. 5, 91:11-22, 107:23-108:3; DTX 17 at D0186, D0216). Had Daiichi sought to mislead the examiner, it could have tampered with the date on the Chemical abstract or the German and English translations of the application. Instead, Apotex has shown only that the date on the 1449 form was typed incorrectly, which is not sufficient to meet the high standard of clear and convincing evidence. SunTiger Inc. v. Scientific Research Funding Group, 194 F.3d 1335 (Fed. Cir. 1999)("[a]rgument alone is not enough to meet the high standard of proof needed to justify a finding of invalidity, namely that of clear and convincing evidence.").

Moreover, on June 15, 1993 the examiner stated that he rejected the '741 patent application because Katz '456 made

[27]The Court is not persuaded by Apotex's contention that the examiner would not have understood the date identified as the "date of disclosure" on the English translation to be the date of publication. (Trial Tr. Smith, Vol. 5, 110:6-117:18). Apotex's speculation into what the patent examiner understood the terms "date of disclosure" to mean does not constitute clear and convincing evidence. Norian Corp. v. Stryker Corp., 363 F.3d 1321, 1329 (citing Kahn v. General Motors Corp., 135 F.3d 1472, 1480 (Fed. Cir. 1998) ("Introspection and speculation into the examiner's understanding of the prior art or the completeness or correctness of the examination process is not part of the objective review of patentability")).

obvious that ofloxacin could be administered topically to treat infections. (DTX 17 at D0294). In that rejection letter, the examiner specifically cited page 31, line 12 of the English translation of Grohe '222, noting that the Grohe patent application shows that ofloxacin is effective for treating otitis. (Id.). The examiner did not state that he did or did not deny the '741 patent on that basis; however, his statement proves that he reviewed the Grohe '222 patent application further supporting the Court's finding that there is no clear basis upon which to find that the examiner was misled by the incorrect typed date.

Other than the one incorrect date of the PTO Form 1449, Apotex has not provided any evidence that Daiichi purposely sought to deceive the examiner. Therefore, the Court finds that there is no clear and convincing evidence that Daiichi engaged in inequitable conduct by making false representations.

Hirota '862

On June 15, 1989 Daiichi made a filing in the '741 prosecution that was accompanied by an IDS disclosing two prior (co-pending), but as yet unpublished, U.S. patent applications filed by other Daiichi inventors. (DTX 17 at D0051-D0053; Trial Tr. Vol. 5, 38:21-23). One of those applications, U.S. Patent Application No. 07/133,975, ultimately matured into Hirota '862. (DTX 28 cover page, left column; Trial Tr. Smith, Vol. 6, 9:1-

17). The patent issued on May 8, 1990. (Id.).

Daiichi never disclosed that the Hirota application issued as a patent, which then made it available as prior art. (Trial Tr. Smith, Vol. 5, 62:12-14, 86:2-9, 134:7-13, 135:24-136:11). Moreover, the co-pending patent applications had been sealed when filed to protect their confidentiality. In general, once a patent is issued anything under seal as confidential material would be opened up and would become part of the file history. Ziegler v. Phillips Petroleum Co., 483 F.2d 858,869 (5th Cir. 1973). Yet, no copies of the Hirota application purportedly submitted by Daiichi with the IDS could be found in the file history. (Trial Tr. Killworth, Vol. 8, 8:11-13). Therefore, there is no clear indication that the Hirota patent application was ever considered by the patent examiner. (Id. at 14:19 - 15:4).

Daiichi, however, submitted an additional IDS on February 14, 1992, containing the European version of the ‘862 Hirota patent. (DTX 17 at D109-10; Trial Tr. Smith, Vol. 5, 169:3-6). This patent listed the issue date of the U.S. Hirota patent. (Id.). Along with that IDS, Daiichi provided the examiner with a European Search Report and European Annex, which specifically pointed to the very page and line of the European version of Hirota that Apotex relies on to make its invalidity argument. (DTX 17 at D0180-82; Trial Tr. Smith, Vol. 5, 169:3-9). In

addition, Patent Examiner Jerome Goldberg examined both the applications for the Daiichi '741 and Hirota '862 patents. (PTX 1 at 2; right column; DTX 28, cover page, right column; Trial Tr. Smith, Vol. 6, 10:20-23, 127:4-11; DTX 29 at DSK-18 00869 - EX - bottom of the page; PTX 466). Certain documents in the file history of patent '741 and '862 indicate that examiner Goldberg was reviewing both applications on dates in close proximity with one another. (DTX 17 at D0054-56; Trial Tr. Smith, Vol. 6, 17:6-15).

Apotex has presented no clear and convincing evidence to show that Daiichi intentionally failed to disclose the Hirota patent. Daiichi voluntarily submitted an IDS for the Hirota patent application. Although no one could find the document in the file history, Apotex has put forth no evidence that the absence of the document is a result of Daiichi's wrongdoing. Furthermore, the European version of the Hirota '862 patent, which also was disclosed voluntarily by Daiichi, clearly noted that the '862 patent had been issued. These facts, coupled with the evidence that patent examiner Goldberg was reviewing both the '862 and '741 patent applications at the same time,[28] support the Court's conclusion that deceptive intent has not been established

[28]Although the Court recognizes that examiner Goldberg likely was reviewing over 150 patents during the same time he was reviewing the Hirota and '741 patent applications, in light of all the evidence Apotex has failed to satisfy its burden of showing that Daiichi intended to deceive the examiner. (Trial Tr. Smith, Vol. 6, 39:2-4).

by clear and convincing evidence.

B. Infringement

It is an act of patent infringement under the Hatch Waxman Act for a company to seek FDA approval to market a generic version of a patented drug product or method of treatment prior to expiration of the patent, if the generic version, when marketed, would infringe the patent under an ordinary patent infringement analysis. 35 U.S.C. § 271(e)(2); Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 675 (1990). Apotex agreed to a stipulation that "the method of treating bacterial ear infection by administering generic ofloxacin otic solution, 0.3%, for which Apotex seeks approval in its ANDA No. 76-527, is within the scope of . . . claims 1,2,4,5, and 6 [of the '741 patent] and those claims in the '741 patent read on the proposed use described in Apotex's ANDA No. 76.527." (PTX 313 ¶ 1).

Apotex recognizes that in light of this stipulation, any discussion regarding infringement is irrelevant, because Apotex has essentially conceded that it has infringed patent '741, unless the Court finds that the patent is invalid or unenforceable.[29] See, e.g., Defendants' Response to PPCL 25

[29]Apotex, however, has not conceded that it infringes upon Claims 3 and 7 of the '741 patent. Apotex argued that because it amended the indications on its package insert and product labeling in June 2, 2004 to exclude the indication for otitis externa, it has not infringed on Claim 3 of the '741 patent or induced the infringement of that claim. Since Daiichi, withdrew with prejudice its claim that Apotex's ANDA No. 76-527 infringes

("Moreover, the statement [regarding Apotex's infringement of the '741 patent] is irrelevant in light of the parties' stipulation (PTX 313). Finally, there can be no liability for infringement of an invalid claim."). Because the Court already has determined that the '741 patent is not invalid as anticipated or obvious and is not unenforceable due to Daiichi's alleged inequitable conduct, Apotex has infringed the '741 patent.

III. CONCLUSION

For the reasons stated in this Opinion, this Court finds that Daiichi's '741 patent is not invalid as anticipated or obvious or unenforceable for inequitable conduct. Furthermore, the Court concludes that Apotex has infringed claims 1,2,4,5 and 6 of the '741 patent.

An appropriate Judgment accompanies this Opinion.

/s/ William G. Bassler
WILLIAM G. BASSLER, U.S.S.D.J.

Dated: August 1, 2006

Claim 3 of the '741 patent, however, Apotex's argument is irrelevant. See March 28, 2006 Stipulation; supra n.7. Furthermore, Daiichi stipulated that based on the Court's interpretation of Claim 7, Apotex's ANDA No. 76-527 was not within the scope of "the literal language of claim 7 . . . or an equivalent thereof." (PTX 313 at ¶ 4; supra n.7).